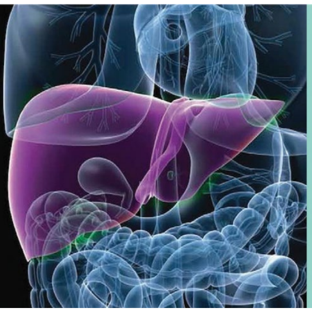

The Impact of Frailty, Sarcopenia, and Malnutrition on Liver Transplant Outcomes

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Frailty, sarcopenia, and malnutrition are critical considerations in the evaluation of patients with cirrhosis who require liver transplantation (LT). The concept of frailty consists of functional decline, vulnerability to health stressors, and decreased physiological reserve.[1] Sarcopenia, defined by a reduction in muscle mass and function, may occur as a result of aging or chronic diseases, including cirrhosis.[2] Malnutrition can further lead to sarcopenia through decreased intake or altered uptake of nutrients, resulting in a change in body mass. Defining these elements in liver disease has not reached consensus, nor have measures of these elements been widely accepted.

In the United States, allocation of liver allografts is based on the Model for End-Stage Liver Disease (MELD) score, which includes key objective laboratory measures of liver and kidney function. Typical pretransplant testing often helps to identify patients at high risk for posttransplant mortality because of other comorbidities, such as cardiopulmonary disease. Frailty, sarcopenia, and malnutrition are additional key factors that should be considered in the transplant evaluation but have been traditionally difficult to formally assess in an objective manner. In this review, we highlight the impact of these factors on posttransplant outcomes, identify methods of assessment, and propose potential optimizing interventions.

FRAILTY

Frailty may be present in up to half of patients awaiting LT.[3] Although the mechanism of frailty in liver disease is

Abbreviations: ADL, activities of daily living; CFS, Clinical Frailty Scale; CI, confidence interval; CPET, cardiopulmonary exercise testing; FFI, Fried Frailty Index; HR, hazard ratio; ICU, intensive care unit; IRR, incidence rate ratio; KPS, Karnofsky Performance Status; L3, third lumbar; LFI, Liver Frailty Index; LOS, length of stay; LT, liver transplantation; MAMC, mid-arm muscle circumference; MELD, Model for End-Stage Liver Disease; OR, odds ratio; RFH-GA, Royal Free Hospital Global Assessment; SGA, Subjective Global Assessment; SMI, skeletal muscle index; SPPB, Short Physical Performance Battery.

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complex, it may result from an impairment across multiple organ systems, including neuromuscular, endocrine, skeletal muscle, immune, and gut microbiome. Measures of frailty exist on a spectrum from strictly objective to more subjective measures. These tests are assessed by patient self-report, physical performance, or provider assessment. Commonly used scoring systems include Clinical Frailty Scale (CFS), Karnofsky Performance Status (KPS), activities of daily living (ADL), Braden Scale, Fried Frailty Index (FFI), Short Physical Performance Battery (SPPB), Liver Frailty Index (LFI), grip strength, gait speed, 6-minute walk test, and cardiopulmonary exercise testing (CPET).[4] The characteristics of each test are highlighted in Table 1.

Severity of frailty in potential transplant recipients correlates with higher mortality rates while on the wait list and is predictive of the likelihood of transplant delisting, hospitalization, posttransplant complications, and depression. A key study by Lai et al.[5] of wait-listed patients with cirrhosis assessed with FFI at outpatient visits found that frailty was significantly associated with increased wait-list mortality and higher likelihood of delisting even after adjusting for severity of liver disease. In addition, this group has subsequently proposed a novel LFI, which assesses grip strength and balance, along with the ability to perform chair stands,[4] and demonstrated that the addition of a frailty index to MELD may improve risk prediction of wait-list mortality.[6] Although the LFI is adjusted for sex and age, the role of ethnicity remains unclear. Although the rate of frailty increases with age, both frailty and advanced age independently correlate with higher wait-list mortality.[7] Current limitations of many performance-based frailty assessments include lack of data in the inpatient setting, as well as the limited ability to assess longitudinal change. Before generalization of testing and management is appropriate, there exists a need for expansion of single-center experiences to multicenter longitudinal evidence. The KPS, which is a provider-based assessment, has been assessed in the inpatient setting and correlates with mortality after LT and diminished graft survival.[8] Furthermore, failure to improve the KPS after LT has correlated with poor survival as well. The Braden Scale, a standardized tool to assess pressure ulcer risk in hospitalized patients, and CPET both correlate with post-LT mortality.[4] Patients deemed high risk by the Braden Scale may also have prolonged hospitalization after LT.

SARCOPENIA

Sarcopenia, or significant reduction in muscle mass, may be present in more than half of patients with cirrhosis and correlates with mortality on the wait list. Although sarcopenia may develop in part because of diminished oral intake in the setting of ascites, other factors may contribute, including degradation of skeletal muscle for gluconeogenesis, low levels of anabolic hormones, and upregulation of myostatin by ammonia. Furthermore, common posttransplant immunosuppressants, including corticosteroids and calcineurin inhibitors, may impede recovery of skeletal muscle.[9]

Quantitative assessment of sarcopenia is possible by analyzing cross-sectional imaging. Common sites of measurement include the third (L3) or fourth lumbar vertebrae, psoas muscle, or total abdominal wall. Several definitions for sarcopenia have been reported, including muscle mass two standard deviations less than the healthy young adult mean. Previously, psoas muscle area had been proposed to define sarcopenia in patients with cirrhosis, with suggested cutoffs of 1561 mm^2 in men and 1464 mm^2 in women.[10] A recent multicenter study by Carey et al.[11] used computed tomographic images of the superior aspect of the L3 vertebra, normalized to height to calculate the SMI (skeletal muscle index), and defined SMI cutoffs for sarcopenia in men and women as less than 50 and 39 cm^2/m^2, respectively. Lower SMI correlated with higher wait-list mortality.

The presence of sarcopenia has been associated with increased wait-list mortality and infection rates, as well as decline in pulmonary and functional status. In fact, Golse et al.[10] reported significantly lower 1- and 5-year survival rates in patients with versus patients without sarcopenia (59% versus 94% and 54% versus 80%, respectively; $P < 0.001$). Furthermore, the majority of studies report an

TABLE 1. COMPONENTS OF FRAILTY ASSESSMENTS USED IN LT EVALUATION

	CFS	KPS	ADL	Braden Scale	FFI	SPPB	LFI	Grip strength	Gait speed	6-Minute Walk Test	Cardiopulmonary Exercise Testing
Provider assessment	✓	✓		✓							
Patient reported	✓	✓	✓	✓	✓						
Physical testing required					✓	✓	✓	✓	✓	✓	✓
Predictive of post-LT outcomes		✓		✓							✓

association between sarcopenia and increased posttransplant mortality, length of intensive care unit (ICU) stays, ventilator dependency, and comorbidities, such as renal events, cardiac events, and even graft failure.[12] Sarcopenia may persist for as much as 1 year after LT and correlates with reduced survival. Furthermore, patients who experience *de novo* sarcopenia after LT may also be at increased risk for death.[13] Posttransplant sarcopenic obesity, which may be difficult to assess clinically, is associated with the presence of metabolic syndrome.[14] Although sarcopenia is associated with adverse events before and after transplantation, the true long-term impact of sarcopenia requires further prospective, multicenter studies using standardized definitions of sarcopenia that are liver disease, sex, and race specific.

MALNUTRITION

The reported prevalence rate of malnutrition in cirrhosis is 40% to 90%.[15] Malnutrition may occur in these patients as a result of decreased nutrient intake, decreased intestinal absorption, and alterations in metabolism.[16]

Current assessment methods include triceps skin fold thickness, mid-arm muscle circumference (MAMC), total body electric conductivity, bioelectrical impedance, and bone density scans. Composite scales, such as the Royal Free Hospital Global Assessment (RFH-GA) and Subjective Global Assessment (SGA), also exist. The RFH-GA is an index of nutritional status combining physical (body mass index, triceps skin fold thickness, MAMC) markers and patient-reported dietary intake. Similarly, the SGA combines patient-based (weight loss, dietary intake, gastrointestinal symptoms, functional status) and physician-based (nutrition requirements, muscle wastage, fat stores, edema) entities. A limitation in using some of these body composition markers is lack of availability, as well as interobserver variability. SGA, in particular, can be assessed through interview as part of the transplant evaluation and has been identified as a reliable tool for LT candidates.[17,18]

Severe malnutrition, like sarcopenia, independently correlates with post-LT infections, sepsis, need for ventilation greater than 24 hours, and duration of ICU stay (Fig. 1). Pre-LT malnutrition may also impact intraoperative blood product needs, overall postoperative length of stay (LOS), and in some cases, mortality.[19-23] Although severe malnutrition, as indicated by the SGA, was associated with increased blood product needs during transplantation, this study was retrospective, and causality cannot be implied.

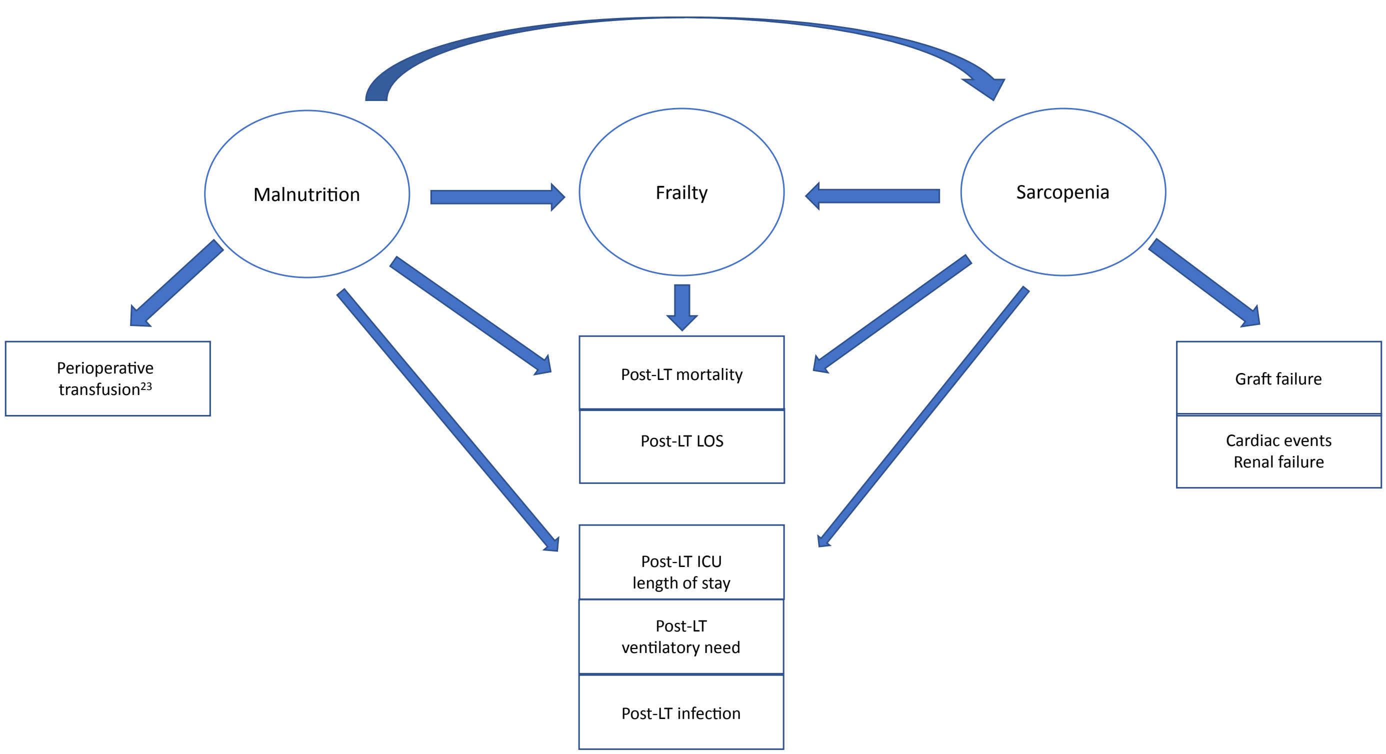

FIG 1 The negative impact of malnutrition, frailty, and sarcopenia on LT outcomes.

TABLE 2. NUTRITIONAL CONSIDERATIONS BEFORE AND AFTER LT[25]

Before LT	After LT
Baseline formal multimodality frailty and nutritional assessment (performance tests, imaging)	Early extubation; early mobilization postoperatively
Assess endocrine comorbidities (diabetes, thyroid, gonadal axis)	Early feeding (enteral preferred) within 12-24 hours postoperatively
Adequate caloric intake (35-40 kcal/kg/day) based on dry weight	10-15 kcal/kg day until postoperative day 3; increased to 25-35 kcal/kg/day by day 5; increase protein intake (1.5-2.0 g/kg/day) during the immediate 4-week period after LT
Adequate protein intake (1.2-1.5 g/kg/day), including branched chain amino acids	Minimize weight gain to avoid obesity and the development of metabolic syndrome
Frequent, small meals with an evening snack	Consider the effects of post-LT immunosuppressants (diabetes, weight gain, decrease in muscle mass)
Prehabilitation, physical therapy, enrolment in a supervised exercise program when indicated	Consider testing and repleting vitamin and mineral deficiencies
Consider testosterone replacement in men with hypogonadism; consider vitamin and mineral supplements	Continued assessment of frailty and nutritional status

We summarize the key studies of various assessment tools and their clinical outcomes in Table 2.

POTENTIAL INTERVENTIONS

Pre-LT nutritional guidance should include encouraging adequate caloric (35-40 kcal/kg/day based on dry weight) and protein intake (1.2-1.5 g/kg/day) (Moss et al.[24] provide more details on this key topic). Patients with ascites and/or anorexia may be advised to consume more frequent, small meals throughout the day. An evening snack containing both carbohydrates and protein may also prevent gluconeogenesis and prevent muscle breakdown. Branched chain amino acids may improve hepatic encephalopathy and muscle cramps.

Although no specific treatments are known to definitively reverse sarcopenia, it is reasonable to pursue interventions to improve skeletal muscle volume and overall strength. Prehabilitation, or pretransplant optimization of physical functionality, should be considered, including formal assessment of frailty and initiation of physical therapy when indicated. Testosterone replacement may be beneficial in men with hypogonadism.

TABLE 3. SUMMARY OF KEY STUDIES ASSESSING TOOLS THAT CAN BE USED TO ASSESS RISK OF POSTTRANSPLANT OUTCOMES

Key Study	Assessment Tool	Method	Outcome
Thuluvath et al.[8]	KPS	Listed patients grouped into three scoring groups and assessed after transplant graft and patient outcome	- More graft failure in intermediate (HR 1.17, 95% CI: 1.12-1.22; $P < 0.001$) and low groups (HR 1.38, 95% CI: 1.31-1.46; $P < 0.001$) - Decreased patient survival in intermediate (HR 1.18, 95% CI: 1.13-1.24; $P < 0.001$) and low groups (HR 1.43, 95% CI: 1.35-1.52; $P < 0.001$) - Failure to improve KPS after transplant was associated with poor survival
Sundaram et al.[26]	Braden Scale	Assigned low, moderate, or high scores	- High risk Braden scale score was associated with: • Prolonged LOS (IRR 1.56, 95% CI: 1.47-1.65) • Nonambulatory status at discharge (OR 4.15, 95% CI: 1.77-9.71) • Discharge to a rehabilitation facility (OR 5.51, 95% CI: 2.57-11.80)
Prentis et al.[27]	CPET	Prospective assessment of 60 patients who completed CPET and underwent LT	- Anaerobic threshold was the only significant predictor of posttransplant mortality in multivariate analysis - Optimum anaerobic threshold: >9 mL/min/kg
Esser et al.[28]	Cross-sectional area of the psoas muscle	Identified patients with and without sarcopenia and assessed 1- and 3-year patient and graft survival	- Preoperative sarcopenia was associated with increased patient mortality (OR 3.84, 95% CI: 1.09-13.59; $P <$ 0.001)- Preoperative sarcopenia was associated with increased graft loss (OR 5.40, 95% CI: 1.85-15.77, $P <$ 0.01)
Merli et al.[19]	Global nutritional assessment, anthropometry	Prospective assessment of 38 consecutive LT recipients	- Malnutrition was significantly associated with LOS and total number of hospital days, as well as number of infections

Sarcopenia may persist after transplant and even develop *de novo* post-LT in some patients. Furthermore, sarcopenia may be present but difficult to diagnose in obese LT patients. Post-LT immunosuppression may further hinder recovery of muscle mass. Assessment of nutritional status begins before transplant and requires ongoing, continued monitoring posttransplant (Table 3).

CONCLUSIONS

Frailty, sarcopenia, and malnutrition clearly impact pre- and post-LT morbidity and mortality. Incorporating these factors in the pre-LT evaluation will undoubtedly help to assess transplant candidacy and potentially may be used for prioritization for transplant. Although pre-LT management is necessary to prevent death while on the wait list and improve post-LT outcomes, recognizing that sarcopenia and malnutrition may persist after transplant is equally critical. Although multiple measures exist, more work is needed to determine optimal standardized assessments and targeted interventions.

TEACHING POINTS

1. Frailty, sarcopenia, and malnutrition play important roles in the prognosis and natural history of end-stage liver disease, before LT, in the perioperative period, and after transplant, independent of the severity of liver dysfunction.
2. Transplant evaluation should include standardized assessments of nutritional health to improve our prediction of transplant-related outcomes.
3. Although not backed by definitive evidence, interventions to ensure adequate caloric and protein intake, as well as prehabilitation, should be considered in the transplant evaluation process.

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